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Finnegan Henderson Farabow
Garrett & Dunner
1300 I Street NW
Washington, DC 20005

EXAMINER	
BRANNOCK, MICHAEL T	
ART UNIT	**PAPER NUMBER**
1646	

DATE MAILED: 02/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/786,033	PAUSCH ET AL.	
	Examiner	Art Unit	
	Michael Brannock	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) *8,10-12,14-19 and 25-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-7,9, 13, 20-24,28 and 29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *010301, 112901*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application: Claims and Amendments

Claims 8, 10-12, 14-19, 25-27 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the response of 10/31/03. Applicant's traversal is on the grounds that the instant claimed modifications are to wild-type receptor sequences, and they are not replacement of portions of the native receptor sequences with the corresponding domain of a yeast G-protein coupled receptor as taught by the prior art Sledziewski patent. This argument has been fully considered but not deemed persuasive.

13.2 *Circumstances in Which the Requirement of Unity of Invention Is to Be Considered Fulfilled*:

Where a group of inventions is claimed in one and the same international application, the requirement of unity of invention referred to in Rule 13.1 shall be fulfilled only when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features. The expression "special technical features" shall mean those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art.

The analysis for lack of unity focuses on only the single independent claim and unity of invention can be found to be lacking within an independent claim, see PCT Rule 13.3 In the instant case, claim 1 recites the technical feature shared by the other claims which is identified as the limitation "wherein the modification comprises a mutation in an intracellular domain of the G-protein coupled receptor and results in an improved functional response in a cell-based assay as compared to a wild-type form of the heterologous G-protein coupled receptor". The teachings of Sledziewski read on this claim because the claim encompasses such substitution mutations as

taught by Sledziewski. In fact, Claim 15 directly reads on such substitution mutations. Thus the technical feature of the independent claim is not a special technical feature as defined by PCT Rule 13.2 as it does not define a contribution over the prior art. Thus, the holding of lack of unity is deemed to be proper and is made FINAL.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-7, 9, 13, 22-24, 28 and 29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, for the following reasons.

Claim 1 (and dependent claims) requires a "modification" wherein the modification "comprises" a mutation. The word "comprises" sets open bounds to the word "modification" and thus renders the claims indefinite because the artisan would not know what other, if any, features are to accompany the mutation to constitute the "modification".

Claims 1, 4-7, 9, 13, 20, 21, 24, 28, and 29 require that the receptor have "an improved functional response" yet the claims do not stipulate what function is to be improved. The specification does teach the artisan how to identify which properties are to be considered "functions" and which are not. Therefore, an artisan would not be reasonably appraised of the bounds of these claims.

In claim 22, "the modification" lacks antecedent basis, so that the artisan would not know either which modification is "the modification" nor what the metes of the term is supposed to encompass.

In claim 29, regarding the phrase "the deletion is IC3Δ", one skilled in the art might interpret this to mean that the entire intracellular third loop has been deleted, however the specification implies, but does not state, that the term IC3Δ refers to any deletion in the third intracellular loop and need not be interpreted as limited to the deletion of the entire loop (e.g. page 3). It is suggested to Applicant, that if it is the latter meaning that is appropriate, then the phrase "the deletion is an IC3Δ" would encompass many types of deletions in the third intracellular loop.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 3, 4, 5, 6, 7, 9, 21, and 29 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 96/00739, to Strader, published January 11, 1996.

Strader disclose an assay using yeast cells (pg 9) wherein the rat M3 muscarinic acid receptor is mutated in the third intracellular domain by deletion of at least one amino acid (pge 13, L24-30) resulting in enhanced function of the receptor in a cell based assay, i.e. the receptor binds the ligand with high affinity in the absence of G-protein (pg 13, L3-L14). Further, as admitted in the instant specification, e.g. page 3, such a mutation would be expected to interfere with the cell desensitization or sequestration-internalization machinery, absent evidence to the contrary. It is noted that on pg 13 L10-14 Strader teaches away from the expectation that such deletions would improve functional coupling of the receptor to the G-protein.

Claims 1 and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No: 5576210 to Sledziewski, published 11/19/1996.

Sledziewski teach a yeast cell comprising a nucleic acid sequence encoding a modified heterologous GPCR, wherein the modification comprises a mutation in an intracellular domain of the GPCR and results in an improved functional response in a cell based assay as compared to wild-type, and wherein the modified GPCR is a muscarinic acetylcholine receptor (see the Abstract and col 3), and wherein the measuring effect of the test compound is measuring growth (see col 4).

Claim1-7, 20-24, 28, 29 are rejected under 35 U.S.C. 102(a) and 102(e) as being anticipated by U.S. Patent No: 5789184, to Fowlkes, published Aug. 4, 1998, filed June 5, 1995 which claims priority to application 08041431, filed March 31, 1993.

Fowlkes disclose yeast cells comprising a nucleic acid encoding a GPCR (e.g. a muscarinic receptor, that may be mutated, Col 26, L19-L25) that has been modified as a matter of routine optimization of operating parameters, i.e. such that it is improved in its functions in a cell based assay as compared to wild-type, (col 15, L29-L63), wherein the modification comprises a deletion is in one of the loops of the GPCR (col 15, L57). One of ordinary skill in the art would understand from the teachings of col 15 that the reference to "loops" at line 57 necessarily includes the third intracellular loop because it is only one of six loops. Further, the functionality of the modification is clearly taken to be an improvement in the agonist-induced growth of the cells, see col 10, L27-44.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 2 is rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No: 5576210 to Sledziewski, published 11/19/1996 in view of W0 92/05244, to King, published 4/2/1992.

Sledziewski teach a yeast cell comprising a nucleic acid sequence encoding a modified heterologous GPCR, wherein the modification comprises a mutation in an intracellular domain of the GPCR and results in an improved functional response in a cell based assay as compared to wild-type, and wherein the modified GPCR is a muscarinic acetylcholine receptor (see the

Abstract and col 3), and wherein the measuring effect of the test compound is measuring growth arrest, a negative effect, (see col 4) or the or the induction of LacZ, a positive effect (col 3). Claim 2 however requires that the agonist increase growth. King et al. describe an identical assay where the effect of an agonist would be to either to induce LacZ or HIS3, see page 10, L14. It is old and well established that the HIS3 gene is used as an indicator gene because its induction allows yeast to grow on media lacking histidine; thus one of ordinary skill in the art would understand that King intends that the HIS3 gene would be used to produce agonist-induced growth of cells.

Therefore, it would be obvious to one of ordinary skill in the art at the time the invention was made to use HIS3 as a reporter gene as taught by King in the assays taught by both King and Sledziewski wherein the GPCR comprises a modification as taught by Sledziewski. The motivation to do so is provided by King who teach that the assay can be performed with HIS3 as the reporter gene in addition to LacZ.

Claim 9 is rejected under 35 U.S.C. 103(a) as being anticipated by U.S. Patent No: 5576210 to Sledziewski, published 11/19/1996 in view of Bonner et al., Science 237(527-537)1987.

Sledziewski teach a yeast cell comprising a nucleic acid sequence encoding a modified heterologous GPCR, wherein the modification comprises a mutation in an intracellular domain of the GPCR and results in an improved functional response in a cell based assay as compared to wild-type, and wherein the modified GPCR is a muscarinic acetylcholine receptor (see the Abstract and col 3. Sledziewski do not specifically mention that the muscarinic acetylcholine

receptor should be the rat M3 receptor. Bonner et al. (1987) describes the cloning of the rat M3 muscarinic receptor, see the Abstract and Figure 1. Therefore, one of ordinary skill in the art, at the time the invention was made, and with reasonable expectation of success, would be motivated to use the rat M3 muscarinic acid receptor as taught by Bonner when practicing the invention of Sledziewski. The motivation to do so is taught by Sledziewski teach that muscarinic acid receptor should be used in the invention, and by Bonner who provide the receptor.

Claim 9 is rejected under 35 U.S.C. 103(a) as being anticipated by U.S. Patent No: 5789184, to Fowlkes, published Aug. 4, 1998, filed June 5, 1995 which claims priority to application 08041431, filed March 31, 1993 in view of Bonner et al., Science 237(527-537)1987.

Fowlkes disclose yeast cells comprising a nucleic acid encoding a GPCR (e.g. a muscarinic receptor, that may be mutated, Col 26, L19-L25) that has been modified as a matter of routine optimization of operating parameters, i.e. such that it improved in its functions in a cell based assay as compared to wild-type, (col 15, L29-L63), wherein the modification comprises a deletion is one of the loops of the GPCR (col 15, L57). One of ordinary skill in the art would understand from the teachings of col 15 that the reference to "loops" at line 57 necessarily includes the third intracellular loop because it is only one of six loops. Further, the functionality of the modification is clearly taken to be an improvement in the agonist-induced growth of the cells, see col 10, L27-44.

Fowlkes et al. specifically teach that a GPCR from any origin can be used in the invention (e.g. col 14, line 47) and also that proteins described in Bonner et al. (1987) can be

used (col 81), however, Fowlkes do not specifically mention the rat M3 muscarinic receptor. Bonner et al. (1987) describes the cloning of the rat M3 muscarinic receptor, see the Abstract and Figure 1. Therefore, one of ordinary skill in the art, at the time the invention was made, and with reasonable expectation of success, would be motivated to use the rat M3 muscarinic acid receptor as taught by Bonner when practicing the invention of Fowlkes. The motivation to do so is taught by Fowlkes who state that a protein from any origin can be used and who specifically point to the Bonner reference.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 13 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a modification that results in a 44 amino acid third intracellular loop comprising the 22 residues proximal to the 5th and the 6th transmembrane domains, does not reasonably provide enablement for other modification resulting in a 44 amino acid third intracellular loop. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The specification indicates that deletions can be made to a variety of GPCRs wherein the remaining third intracellular loop comprises the 22 residues proximal to the 5th and the 6th transmembrane domains, resulting in a 44 amino acid third IC loop (e.g. Examples 1-4). This is a very specific teaching, yet the claims encompass any of a practically infinite

number of deletions – which only need to result in a 44 amino acid third IC loop. The specification has not taught a method for the artisan to use to discover other such deletion strategies and has only offered the artisan an invitation to randomly try to find such.

The claim is, in essence, single means claim, because the claim encompasses any composition having the recited activities whereas the instant specification only discloses the single composition known to the inventor. In *In re Hyatt*, 708 F.2d 712, 218 USPQ 195 (Fed. Cir. 1983), a single means claim which covered every conceivable means for achieving the stated purpose was held nonenabling for the scope of the claim because the specification at most disclosed only those means known to the inventors. When claims depend on a recited property, a fact situation comparable to *Hyatt* is possible, where the claim covers every conceivable structure (means) for achieving the stated property (result) while the specification discloses at most only those known to the inventor. See also *Fiers v. Sugano*, 984 F.2d 164, 25 USPQ2d 1601 (Fed. Cir. 1993), and MPEP § 2164.08(a). The skilled artisan would not expect to readily find such other deletion mutants. As indicated above, the prior art demonstrates that many deletions diminish the efficiency G-protein activation – a property that is asserted to be necessary for the instant invention, see page 3 of the instant specification and pg 13 L10-14 of Strader (WO 96/00739) who teaches away from the expectation that such deletions would improve functional coupling of the receptor to the G-protein.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Brannock, Ph.D., whose telephone number is (571) 272-0869. The examiner can normally be reached on Mondays through Fridays from 10:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, Ph.D., can be reached at (571) 272-0871.

Official papers filed by fax should be directed to (703) 872-9306. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

MB

February 3, 2004

GARY KUNZ
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600